REMARKS/ARGUMENTS

Claims 1-78 are pending in the application. Claims 3, 9, 13, 16-19, 22, 24, 30, 34, 36-41, 48, 50, 55-56, 60, 64-65, 67, 69, 71-76 and 78 have been amended. Claims 79-82 have been newly added. Entry of the amendment, reconsideration of the rejection, and allowance of claims 1-82 are respectfully requested.

The Amendment

In order to expedite prosecution of the application and advance the case toward allowance, the claims have been amended. Claims 3, 9, 13, 16-19, 22, 24, 30, 34, 36-41, 48, 50, 55-56, 60, 64-65, 67, 69, 71-76 and 78 have been amended to correct for proper antecedent basis as supported in the claims and specification.

Claims 13, 37 and 69 have been amended to delete the term "preferentially" for being allegedly indefinite.

Claims 17-18, 38-39, 60 and 73-74 have been amended to correct for proper claim dependency.

Claim 56 has been amended to specify that force is applied to the tooth. Support for this amendment can be found, for example, on page 2, lines 12-14.

Claim 78 has been amended to replace the term "relaxin" with "a relaxin composition". Support for this amendment can be found, for example, on page 4, paragraph [0011] and page 6, paragraph [0017]. No new matter was introduced by this amendment.

New claim 79 finds support, for example, on page 4, paragraph [0011], line 19.

New claim 80 finds support, for example, on page 2, paragraph [0006], line 11 and page 3, paragraph [0009], line 23.

New claim 81 finds support, for example, on page 3, paragraph [0009], line 30.

New claim 82 finds support, for example, on page 12, paragraph [0063], lines 21-22.

Claim Objections

Claims 25 and 60 are objected to because of improper dependent form. The claim dependency has been corrected accordingly.

Claim 24 has been amended to specify that the substance comprises an angiogenic substance selected from the group consisting of VEGF, bFGF, estrogen, nitrous oxide and naltrexone. Hence, claim 25 now further limits claim 24.

Claim 60 has been amended to depend from claim 59. As such, claim 60 now further limits claim 59.

In light of the corrections above, Applicants respectfully request that the objections be withdrawn.

Double Patenting

The Office Action indicates that if claim 23 were found to be allowable, claim 24 would be objected under 37 CFR §1.75 as being a substantial duplicate thereof.

Claims 24 has been amended to specify that the substance comprises an angiogenic substance such as VEGF, bFGF, estrogen, nitrous oxide or naltrexone. As a result, claims 23 and 24 now differ from one another.

In light of this correction, Applicants respectfully request that the objection be withdrawn.

Rejection Under 35 U.S.C. §112

Claims 13, 34, 61-64, 67-69 are rejected under 35 U.S.C. §112, second paragraph, as being allegedly indefinite. In the interest of prosecution efficiency, the claims have been amended accordingly. However, this amendment is made to advance the claims toward allowance and should not be construed as an acquiescence in the rejection.

Claim 13, 34 and 69 have been amended to delete the term "preferentially" for being allegedly indefinite as indicated by the Examiner.

Claims 61-64 and 67-68 have been rejected for lacking proper antecedent basis with respect to the terms "applying force" and "the force". Since, claims 61-64 and 67-68

depend on claim 56, claim 56 has been amended to specify that "force is applied to the tooth". Thus, claims 61-64 and 67-68 now have proper antecedent basis.

In light of these corrections, Applicants respectfully request that the rejection of claims 13, 34, 61-64, 67-69 under 35 U.S.C. §112, second paragraph, be withdrawn.

Rejection Under 35 U.S.C. §101

Claim 78 has been rejected as being directed to non-statutory subject matter since the claim is allegedly directed to a naturally occurring article such as relaxin. The rejection is respectfully traversed.

The claim has been amended to recite "a relaxin *composition* or analog or mimetic thereof". Support for this amendment can be found, for example, on page 4, paragraph [0011] and page 6, paragraph [0017]. Relaxin, as referred to in the instant invention, includes a relaxin composition used to reposition teeth by applying force. This is clearly explained on page 4, paragraph [0011] and on page 6, paragraph [0017], wherein various compositions are discussed. For example, in pargraph [0011], line 18, the specification indicates that the substance of the instant invention may be prepared in a conventional form of topical composition, such as a gel, cream, ointment, or other fluid or liquid substance. In paragraph [0017], line 26, the specification indicates that topical oral compositions comprise a carrier and a tissue remodeling and/or an angiogenic substance; and that the carrier is of the type which may be topically applied to a patient's gingiva, typically being in the form of, for example, a gel, cream, ointment, microemulsion or other liquid.

In light of this amendment, Applicants respectfully request that the rejection of claim 78 under 35 U.S.C. §101, be withdrawn.

Rejection Under 35 U.S.C. §102

Claims 56, 58, 70 and 78 are rejected under 35 U.S.C. §102(b), as being allegedly anticipated by Nicozisis *et al.* To the extent that the rejection is applied to the claims as amended, the rejection is respectfully traversed.

"In order for a rejection under §102(b) to be valid, each and every element of the claim must be found in the prior art reference."[1]

Claim 56 has been amended to clarify that the method includes *applying force to said tooth*. Claims 58 and 70 depend on claim 56. Claim 78 has been amended to refer to a relaxin *composition* or analog or mimetic thereof.

Nicozisis *et al.* investigate the effects of relaxin on cranial sutures in mice. They show that the periodontal ligament (PDL) of the samples treated with relaxin displays an irregular organization and loose arrangement from tooth to bone surface. However, Nicozisis *et al.* do not discuss the effect of relaxin on PDL when force is applied. In fact, Nicozisis *et al.* indicate on page 198 (first column, last paragraph) that **mechanical perturbation was not included in the experimental protocol as it was not within the scope of the study**. They further suggest that relaxin's effect on the rate of tooth movement *may be* investigated along with the tendency for relapse once the tooth is moved or rotated (second column, first paragraph). Yet, Nicozisis *et al.* present no data to that effect. Thus, Nicozisis *et al.* do not anticipate the claimed invention.

In light of the above amendment and remarks, Applicants respectfully request that the rejection of claims 56, 58, 70 and 78 under 35 U.S.C. §102(b), be withdrawn.

Rejection Under 35 U.S.C. §103

A. Claims 1-8, 10-19, 22-29, 31-40, 57-64, 66-69, 71-75 are rejected under 35 U.S.C. §103(a), as being allegedly obvious over Nicozisis *et al.*

The Office Action contends that Nicozisis *et al.* indicate on page 198 that "perhaps better demonstrative strains [larger than mice] could be employed to show the effects on relaxin on the connective tissue of the craniofacial complex if mechanical manipulation of the sutures or PDL is an objective...." and "there appears to be a potential application for relaxin as an adjunct to orthodontic therapy". Based on these speculations, the Examiner appears to

[1] MPEP 2131; *In re Royka and Martin,* 180 USPQ 580 (CCPA 1974).

conclude that it would have been obvious for one skilled in the art to administer relaxin during orthodontic treatment of the instant invention.

The rejection is respectfully traversed.

It is well understood that in order to properly maintain an obviousness rejection, three basic criteria must be met. In fact, the MPEP[2] states the following:

"To establish *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations."

I. No Motivation To Modify The Reference:

As indicated above, Nicozisis *et al.* did not investigate the effect of relaxin on PDL when force is applied (*supra*). Besides the indication that **mechanical perturbation was not within the scope of the study,** Nicozisis *et al.* further contend that although there appears to be a potential application for relaxin as an adjunct to orthodontic therapy, *it will be necessary* to study specific collagen types and collagenases *to get a full picture* of the effects of relaxin (see page 199, second column, second paragraph). Notably, when Nicozisis *et al.* pose the question if there could be an utility for relaxin in dentofacial orthopedics, they simply say that it is possible (see page 199, first column, second paragraph). There is no indication whatsoever, that Nicozisis *et al.* have evidence that goes beyond mere speculation. In fact, Nicozisis *et al.* presented no data to whether there is actual utility for relaxin in dentofacial orthopedics. As a result, there is simply no motivation to consult Nicozisis *et al.* in order to arrive at the instant invention. The Office Action appears to assert that it would have been obvious for one skilled in the art to administer relaxin during orthodontic treatment solely based on Nicozisis *et al.'s* speculation that it could be possible. It is respectfully indicated that "the teaching or suggestion to make the claimed combination *and* the reasonable expectation of success must both be found in the prior

[2] see MPEP 2143

art, not in applicant's disclosure". [Emphasis added.] Please see *In re Vaeck*[3]. A reference that serves merely as an invitation to experiment does not render an invention obvious. Thus, Applicants respectfully request that the rejection be withdrawn.

II. No Expectation of Success:

Since Nicozisis *et al.* presented no data as to whether there is actual utility for relaxin in dentofacial orthopedics, there is simply no motivation to consult Nicozisis *et al.* in order to arrive at the instant invention nor would there be a reasonable expectation of success in doing so. Nicozisis *et al.* used mice to demonstrate that endogenous relaxin was present in *cranial sutures*. However, Nicozisis *et al.* also indicate on page 193 that the peridontium was not used for determining the presence of endogenous relaxin because the samples were too hard to cut into sections, instead they used sections of cranial (frontal) sutures (see page 193, second column, third paragraph).

Nicozisis *et al.* further prepared an organ culture from mouse calvariae and mandibles (see page 194, first column, first paragraph), wherein relaxin hormone was added to the medium. They then stained the sections of mouse calvariae (sagittal suture) and mandibles (distal of the incisor to distal of the molar) with epoxy tissue stains (see page 194, first column, last paragraph). Their results on page 194 indicate that endogenous relaxin was indeed present in cranial sutures, however, no *immunohistochemical* staining was performed on the mandible samples as the tissue proved to be too hard for sectioning, thus, **the mandible samples were not included in the analysis** (see page 194, second column, last paragraph). On page 195, Nicozisis *et al.* then discuss their *histological* staining results, including the mandibles. They found that peridontium (PDL) of the samples treated with relaxin showed irregular organization of collagen fibers while the fiber arrangement in the sagittal tissues was difficult to determine. From these results they concluded that the histological evidence in this study exhibits positive effects of relaxin on the connective tissue within the PDL and cranial sutures, mainly because connective tissue fibrils that exhibit a certain directionality became amorphous and random in nature (see page 197, second column, second paragraphs).

[3] *In re Vaeck,* 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

The Examiner appears to suggest that from these findings alone (*i.e.*, findings that exclude any knowledge to whether or not endogenous relaxin is even present in the PDL) one could arrive at the instant invention. Yet, there is no conceivable reason why the Applicants would have any expectation of success by following these teachings. Nicozisis *et al.* do not provide enough information why relaxin had the effect of randomizing tissue fibrils in the PDL nor did they correlate these findings to the presence of enogenous relaxin in the PDL. In fact, Nicozisis *et al.* do not know if endogenous relaxin is present in the PDL, nor do they know if randomized tissue fibrils are the result of an artifact, since they used no negative controls. In the absence of negative controls (*e.g.*, treatment with other hormones or factors) one would not necessarily know if the randomized tissue fibrils are indeed the result of relaxin treatment or simply the result of any treatment. Nicozisis *et al.* then attempt to correlate their findings to Sherwood *et al.* who investigated symphyses of guinea pigs and Cheah *et al.* who investigated rat cervix (see page 197, second column, third paragraph). However, neither of these references have anything to do with PDL, these references refer to collagen arrangement in the cervix wherein the presence of relaxin has long been established (see Cullen *et al.* (1960) *J. Physiol.* 152:419-36, "The effect of hormones on the physical properties and collagen content of the rat's uterine cervix"). Notably, Nicozisis *et al.*'s study sought to demonstrate the presence of relaxin hormone within the sagittal suture of the cranium (see page 197, first column, last paragraph) and did not use the mandible for immunohistochemistry **"because the hardness of the tissue (bone and tooth) would have been impossible to section"** (see page 197, second column, first paragraph). Hence, there is simply no motivation to modify Nicozisis *et al.*, to arrive at the present invention. Accordingly, Applicants respectfully request that the Examiner withdraw the rejection.

III. The Cited Reference Does Not Teach All the Elements of the Pending Claims:

It is also well established that all limitations of the claims must be disclosed by the combination of references [or reference] cited as the prior art in order to establish *prima facie* obviousness (MPEP 2143.03). The pending claims specify that in the instant method, a substance such as relaxin is administered to the patient and force is applied to a least one tooth.

But Nicozisis *et al.* do not disclose or even suggest the effect of relaxin on a patient *when force is applied to a tooth.* In addition, no data was presented as to whether there is utility for relaxin in dentofacial orthopedics nor for relaxin in dentofacial orthopedics *when force is applied.* Hence it is clear that Nicozisis *et al.* do not teach all the limitations of the claims. Applicants respectfully request that the Examiner withdraw the rejection.

Unexpected Results:

MPEP 2144.08 states that rebuttal evidence may include evidence that the claimed invention yields unexpectedly improved properties or properties not present in the prior art; and that office personnel should consider all rebuttal arguments and evidence presented by applicants.

The inventors have shown that treatment with relaxin leads to a ***significant*** increase in orthodontic tooth movement, wherein it promotes remodeling of periodontal and gingival tissue to allow for repositioning teeth in a patient as described in the specification; and further that there is a role for relaxin in preventing relapse as discussed in the specification (see attached declaration by Dr. Dennis R. Stewart under 37 CFR §1.132, the "Stewart Declaration").

On page 2 of the declaration, Dr. Stewart declares that his team showed that they were able to use relaxin in combination with force to accelerate orthodontic tooth movement in rats. In this study, one group of animals received implanted relaxin pumps (*i.e.,* continuous relaxin administration) while another group received relaxin injections (*i.e.,* subcutaneous injections on day 1 and day 7 of the treatment period). The rats were treated for 14 days. The results of the two relaxin groups (pump *vs.* injection) were similar and the data from the two groups was combined and graphed against the untreated control group (see Figure 2 on page 3 of the Stewart Declaration). As shown in Figure 2, the relaxin treatment resulted in a *significantly* greater space between the molars in the relaxin treated animals compared to the control animals ($p = 0.0323$). In paragraph 6 of the declaration, Dr. Stewart declares that relaxin treatment helped move the tooth further in the same amount of time than in the control animals. These results not only confirmed the hypothesis that relaxin when used with force would increase the rate of tooth movement, but also provided strong evidence that the rate of tooth movement is

actually significant compared to the control. The significant gap between the molars as a result of relaxin treatment denotes unexpectedly good results. Thus, the inventors have established through clear scientific evidence that relaxin treatment with applied force can significantly speed orthodontic tooth movement.

On page 4 of the declaration, Dr. Stewart's research team further demonstrated that relaxin can be used to prevent relapse in dogs. Relapse occurs when teeth return to their initial position after orthodontic treatment with dental braces or other type of applied force, thus, leading to an unfavorable change from their corrected position. An experiment was designed, wherein one group of dogs (*i.e.*, injected group) had gingival relaxin injections on days 50 and 55, while another group (*i.e.*, control group) had placebo injections. The last group (*i.e.*, fiberotomy group and positive control group) had a gingival fiberotomy on day 55. Fiberotomy is a procedure in which the gingival fibers attached to the tooth are cut down to the alveolar bone (see Figure 5 of the Stewart Declaration, page 5). Fiberotomy is known to be effective in prevention of relapse in dogs and was used a positive control. Alignate impressions were obtained from the dogs and models were cast. The research team used digital pictures of the models to measure the amount of rotation of the second maxillary incisor and its relapse. As Dr. Stewart declares and as shown on the graph in Figure 6 (see page 6 of the Stewart Declaration), the control group had relapse (~30%) as expected and the fiberotomy and positive control group had significantly less relapse ($p = 0.014$) than the control group. The injected group had results intermediate between the negative (control group) and positive (fiberotomomy and positive control group) groups. As set forth in the declaration on page 5, paragraph 9, this effect occurred with only two doses of relaxin which indicates that a slightly higher dose of relaxin administration will lead to a more effective treatment in preventing relapse. As such, Applicants have shown that relaxin treatment can be used to prevent relapse.

These findings underscore the teachings of the invention and establish that the treatment with relaxin with applied force leads to a significant increase in orthodontic tooth movement as well as that there is a role for relaxin in preventing relapse.

In light of the above remarks, Applicants respectfully request that the rejection of claims 1-8, 10-19, 22-29, 31-40, 57-64, 66-69, 71-75 under 35 U.S.C. §103(a), be withdrawn.

B. Claims 9, 30 and 65 as well as claims 43-46, 48 and 51-55 are rejected under 35 U.S.C. §103(a), as being allegedly obvious over Nicozisis *et al.* as applied to claims 8, 29 and 64, and further in view of Kuo *et al.* (U.S. Patent No. 6,607,382).

The Office Action indicates that it would have been obvious to use a removable orthodontic appliance that includes a reservoir as taught by Kuo *et al.* with the method of repositioning teeth and applying relaxin suggested by Nicozisis *et al.* in order to apply the relaxin concurrently with tooth repositioning and to enhance tooth movement and stability.

The rejection is respectfully traversed.

As shown above, Nicozisis *et al.* do not anticipate the instant invention because Nicozisis *et al.* do not disclose a method wherein teeth are repositioned or remodeled by applying a force and administering a substance like relaxin. Furthermore, the instant invention is not obvious over Nicozisis *et al.* because Nicozisis *et al.* have no data as to whether there is actual utility for relaxin in dentofacial orthopedics. Nicozisis *et al.'s* mere speculation that there could be a role for relaxin as an adjunct to orthodontic therapy based on inconclusive data would not have motivated the skilled artisan to modify Nicozisis *et al.'s* teachings. Thus, Nicozisis *et al.'s* disclosure coupled with the knowledge that an *orthodontic appliance with a reservoir* can be used to administer a therapeutic or cosmetic substance to teeth concurrently with movement of the teeth as taught by Kuo *et al.* does not teach all the features of the claims. There is simply no motivation to combine the references because there is no suggestion to do so.

In light of the above remarks, Applicants respectfully request that the rejection of claims 9, 30, 43-46, 48, 51-55 and 65 under 35 U.S.C. §103(a), be withdrawn.

C. Claims 20, 21, 41, 42, 76 and 77 are rejected under 35 U.S.C. §103(a), as being allegedly obvious over Nicozisis *et al.* as applied to claims 1, 22 and 56 and further in view of Korostoff *et al.* (U.S. Patent No. 4,153,060).

The Office Action alleges that it would have been obvious to apply an electric current to the periodontal tissue as taught by Korostoff *et al.* with the method of repositioning teeth and applying relaxin as suggested by Nicozisis *et al.* in order to further enhance bone growth and tooth movement.

The rejection is respectfully traversed.

As shown above, Nicozisis *et al.* do not anticipate the instant invention because Nicozisis *et al.* do not disclose a method wherein teeth are repositioned or remodeled by applying a force and administering a substance like relaxin. In addition, the instant invention is not obvious over Nicozisis *et al.* because Nicozisis *et al.* have no data as to whether there is actual utility for relaxin in dentofacial orthopedics (see comments regarding Nicozisis *et al.* under section B, *supra*). As a result, Nicozisis *et al.'s* disclosure coupled with the knowledge that an *electric current* can be applied to the periodontal tissue to enhance bone growth as discussed in Korostoff *et al.* does not teach or suggest the instant invention. Korostoff *et al.* teach the disposition of an anodic electrode in the direction of applied force at one side of a tooth and a cathodic electrode on the opposite side of the tooth to be moved. They connect a current source to the two electrodes to reposition the tooth (with or without an orthodontic appliance). Clearly, Korostoff *et al.'s* teachings are based on applying an *electrical current* to reposition teeth and has nothing to do with the instant invention. Again, there is no motivation to combine the references. The skilled artisan would not have been able to arrive at the present invention based on the disclosure of Nicozisis *et al.* or Korostoff, nor the combination thereof.

In light of the above remarks, Applicants respectfully request that the rejection of claims 20, 21, 41, 42, 76 and 77 under 35 U.S.C. §103(a), be withdrawn.

D. Claims 43, 47, 49 and 50 are rejected under 35 U.S.C. §103(a), as being allegedly obvious over Burgio (U.S. Patent No. 6,322,360) in view of Nicozisis *et al.*

The Office Action asserts that it would have been obvious to the skilled artisan to use relaxin as the therapeutic agent with the device of Burgio in order to enhance tooth movement and stability as suggested by Nicozisis *et al.*

The rejection is respectfully traversed.

As shown above, Nicozisis *et al.* do not anticipate the instant invention because Nicozisis *et al.* do not disclose a method wherein teeth are repositioned or remodeled by applying a force and administering a substance like relaxin. In addition, the instant invention is not obvious over Nicozisis *et al.* because Nicozisis *et al.* have no data as to whether there is actual utility for

relaxin in dentofacial orthopedics (see comments regarding Nicozisis *et al.* under section B, *supra*). Thus, Nicozisis *et al.'s* disclosure coupled with the knowledge that a device such as an *oral medication delivery tray* as discussed in Burgio can be used to deliver a medication to the teeth does not teach or suggest the instant invention. Burgio discloses a tray assembly in order to deliver a substance to a patient's teeth. The purpose of Burgio's invention is solely to provide a custom fit tray to overcome the shortcomings of mass-produced delivery trays (see column 1, line 40) such that the problem of unintentional separation of the adhesive from the substrate can be avoided (see column 4, line 1-15). Burgio does not teach repositioning teeth nor does he disclose relaxin. Consequently, the skilled artisan would not have been able to arrive at the present invention based on the disclosure of Nicozisis *et al.* or Burgio, neither alone nor in combination with each other.

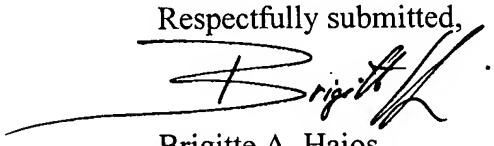
In light of the above remarks, Applicants respectfully request that the rejection of claims 43, 47, 49 and 50 under 35 U.S.C. §103(a), be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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